U.S.S.N. 09/715,965
Filed: November 17, 2000
Amendment

Remarks

Restriction Requirement

Claims 1-18 were divided into two groups, claims 1-11, drawn to a method of using an enzyme, and claims 12-18, drawn to a formulation comprising the enzyme.

Applicants affirm their election of group I, claims 1-11, and cancel claims 12-18.

Applicants also affirm their election of chondroitinase AC and cancer as the species, with the understanding that the generic claim will be searched when the species is otherwise allowable.

Rejections under 35 U.S.C. 112

Claim 1 has been objected to on the basis that "modulate angiogenesis" is unclear. Although it is believed the term "modulate" is clearly understood by those skilled in the art, particularly in view of the specification, the claim has been amended to recite that the enzyme is administered in an effective amount to decrease the ability of tumor cells to proliferate when stimulated by oncogenic growth factors, decrease the ability of tumor cells to invade blood cells, and decrease angiogenesis. Support is found in the application at page 3, lines 1-5, for example.

Rejections under 35 U.S.C. 102

Claims 1-9 were rejected under 35 U.S.C. 102(b) as disclosed by Takeuchi, Br. J. Cancer 26, 115 (1972). This rejection is respectfully traversed.

Takeuchi administers enzyme prior to or with tumor cells injected into mice and shows that the tumor cells do not grow as well. Takeuchi does not demonstrate that one can inject

applicant doesn't require it in claims

enzyme into established tumors and inhibit further growth, nor inhibit angiogenesis – which requires endothelial cells. All of Takeuchi's studies were done solely on and assessing tumor cells. Indeed, the data at col. 1 of page 118 and the discussion at col. 1, of page 119, indicates that the proposed mechanism has nothing to do with angiogenesis. Since he does not demonstrate one can inhibit tumor cell growth by subsequently injecting enzyme, he also does not describe an effective amount of enzyme which would be useful to inhibit tumor cell growth.

This must be contrasted with the data in the application which not only shows efficacy in vivo, but provides dose response curves and assays specifically for inhibition of angiogenesis and inhibition of tumor invasion (not just cell growth). See pages 15-18 and Figures 4-7. See also the experimental data in Example 9, which shows that tumors can be established, as would occur in a normal patient, then treated with injections of enzyme, and significantly reduced in size. Takeuchi does not cause a reduction in size, only a prevention of further growth.

Accordingly, Takeuchi does not anticipate claims 1-9.

Rejection under 35 U.S.C. 103

Claims 1-11 were rejected under 35 U.S.C. 103 as obvious over Takeuchi in combination with JP 51075042. This rejection is respectfully traversed.

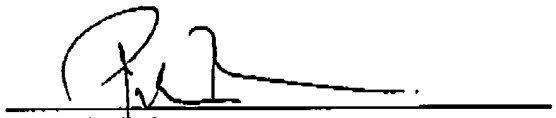
As discussed above, Takeuchi neither discloses nor makes obvious the use of a chondroitin sulfate degrading enzyme to inhibit angiogenesis, nor to reduce tumor size, by administration to an individual in which there are already tumors present.

The JP fails to make up for this deficiency. It is not obvious to administer enzyme to established tumors by any route, or any formulation, when it is not know that one can reduce tumor growth *retroactively*.

The test for obviousness is whether the prior art discloses the claimed elements, and provides the motivation to combine as applicants have done, with a reasonable expectation of success. In the field of cancer, there is no expectation of success based on studies in which tumors are treated *ex vivo*, or at the same time as they are injected into an animal. The literature is repleat with failures based on such data. This data is simply not predictive of success in treating established tumors. Therefore the cited references do not make obvious claims 1-11.

Allowance of claims 1-11, as amended, is therefore earnestly solicited.

Respectfully submitted,



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APPENDIX: Claims marked as Amended

1. (amended) A method to [modulate angiogenesis] decrease tumor growth comprising administering to tumors in an individual in need of treatment thereof an effective amount of a purified glycosaminoglycan degrading enzyme to decrease angiogenesis and thereby reduce tumor growth.

2. The method of claim 1 wherein the enzyme is selected from the group consisting of bacterial glycosaminoglycan degrading enzyme is selected from the group consisting of heparinase 1 from *Flavobacterium heparinum*, heparinase 2 from *Flavobacterium heparinum*, heparinase 3 from *Flavobacterium heparinum*, chondroitinase AC from *Flavobacterium heparinum*, and chondroitinase B from *Flavobacterium heparinum*, heparinase from *Bacteroides* strains, heparinase from *Flavobacterium* Hp206, heparinase from *Cytophagia* species, chrondoitin sulfate degrading enzymes from *Bacteroides* species, chrondoitin sulfate degrading enzymes from *Proteus vulgaris*, chrondoitin sulfate degrading enzymes from *Micrococcus*, chrondoitin sulfate degrading enzymes from *Vibrio* species, chrondoitin sulfate degrading enzymes from *Arthrobacter aurescens*, these enzymes expressed from recombinant nucleotide sequences in bacteria and combinations thereof.

3. The method of claim 1 wherein the enzyme is a mammalian enzyme.

4. The method of claim 1 wherein the enzyme is a chrondroitinase.

5. The method of claim 4 wherein the chondroitinase is chondroitinase AC.

6. The method of claim 1 wherein the individual has cancer.

7. The method of claim 6 wherein the cancer is a solid tumor and the enzyme is chondroitinase AC.

8. The method of claim 1 wherein the individual has a disorder in which angiogenesis is involved, the disorder being selected from the group consisting of rheumatoid arthritis; psoriasis; ocular angiogenic diseases, rubeosis; Osler-Webber Syndrome; myocardial angiogenesis; plaque neovascularization; telangiectasia; hemophiliac joints; angiofibroma; disease of excessive or abnormal stimulation of endothelial cells, Crohn's disease, atherosclerosis, scleroderma, and hypertrophic scars, diseases that have angiogenesis as a pathologic consequence, adhesions, scarring following transplantation, cirrhosis of the liver, pulmonary fibrosis following acute respiratory distress syndrom or other pulmonary fibrosis of the newborn, endometriosis, polyposis, obesity, uterine fibroids, prostatic hypertrophy, and amyloidosis.

9. The method of claim 1 wherein the enzyme is administered systemically.

10. The method of claim 1 wherein the enzyme is administered topically or locally at or adjacent a site in need of treatment.

11. The method of claim 1 wherein the enzyme is administered in a controlled and/or sustained release formulation.

Please cancel claims 12-18.